

SUMMARY
Centers for Disease Control and Prevention (CDC)
Clinician Outreach and Communication Activity (COCA)
Clinician Briefing: TULAREMIA

April 27, 2004

Paul Mead, MD, MPH

Chief of Epidemiology, Microbiology, and Diagnostic Activity
Bacterial Zoonoses Branch, DVBID, NCID, CDC

Jeannine Petersen, PhD

Microbiologist, Diagnostic and Reference Laboratory
Bacterial Zoonoses Branch, DVBID, NCID, CDC

***Please note: Data and analysis discussed in these presentations were current when presented. Data collection and analysis are ongoing in many cases, therefore updates may be forthcoming elsewhere on this website, through publications such as [CDC's Morbidity and Mortality Weekly Report](#) or other venues. Presentations themselves will not be updated. Please bear this in mind when citing data from these presentations*

OVERVIEW

- Tularemia is an uncommon but potentially fatal bacterial zoonosis caused by *Francisella tularensis*. It was first identified in 1911 as a plague-like illness of ground squirrels in Tulare County, CA, hence the name tularemia. The organism now identified as *Francisella tularensis* was isolated in 1912. The first human illness was identified in 1914.
- *Francisella tularensis* is unusual in that it has multiple routes of human infection. The clinical signs and severity of illness depend upon the route of transmission, as well as the specific strain or sub-type of tularemia. The disease is nationally notifiable. National notifiability was discontinued in 1994 because the disease was relatively uncommon; however, it was reinstated by the Council of State and Territorial Epidemiologists in 1999 because of the concerns about intentional use of *Francisella tularensis* as a weapon of bioterrorism.

MICROBIOLOGY

- *Francisella tularensis* is a small, nonmotile, aerobic, gram-negative coccobacillus. It is hardy and non-spore forming. It survives well in water, moist soil, straw, and decaying animal carcasses. There are a variety of virulence factors, but they're poorly understood. Virulence may be enhanced through laboratory manipulations. For example, virulent streptomycin-resistant strains have been evaluated as biowarfare agents, both in the U.S. and in the former U.S.S.R.

SUBSPECIES OF *F. tularensis*

Francisella tularensis can be divided into two major groups or subspecies, also known as biovars, on the basis of virulence testing, biochemical testing and epidemiological factors.

- *F. tularensis*, biovar tularensis, also called Jellison type A. This is considered to be the more virulent form, both for humans and animals, and is generally considered to be the most common biovar in North America. It is typically—although not exclusively—associated with rabbits.

- *F. tularensis* biovar palaeartica type B, which is generally considered to be less virulent and is more common in both Europe and Asia. This particular biovar is more often associated with rodents in aquatic environments, although there are exceptions.

ECOLOGY

- Tularemia occurs in temperate and sub-arctic regions throughout North America and Eurasia, particularly in the Scandinavian countries and Russia. It can be recovered from a wide variety of small mammals and arthropods in North America:
 - wood and dog ticks of the genus *Dermacentor*
 - lone star tick of the genus *Amblyomma*
- Although the true ecology of tularemia in the environment is poorly understood, there are believed to be two main cycles that maintain the organism – one is among lagomorphs (rabbits and hares), with ticks as the main vector. The second main cycle is among rodents and small aquatic mammals. This cycle is believed to be maintained through direct contact between the animals and the environment, especially the water.

TRANSMISSION

- Transmission to humans occurs through a wide variety of mechanisms.
- The main mechanism of transmission in North America is through arthropod bites, including both ticks and deerflies. (Other names for tularemia include deerfly fever and rabbit fever.) In Scandinavian countries, it's believed that tularemia can also be transmitted occasionally through mosquito bites, although we don't have evidence that this occurs in the U.S.
- Tularemia can also be acquired through direct handling of infected tissues or fluids, such as occurs when a hunter skins a rabbit, or through ingestion of contaminated soil, food or water, or through inhalation of infected aerosols; and these can include both agricultural dusts such as hay or straw. This has been seen as the source of several large outbreaks in Scandinavian countries. Inhalation can also occur in the laboratory. When grown on culture plates, *Francisella tularensis* poses a significant hazard to laboratory workers. Despite all these potential modes of transmission, person-to-person transmission has not been documented.

HIGH RISK OCCUPATIONS

- There are a number of occupations that seem to be at higher risk of developing tularemia, including:
 - Microbiologists,
 - Farmers,
 - Veterinarians,
 - Shepherders,
 - Hunters or trappers (particularly, those dealing with rabbits or other small rodents), or
 - Those who handle meat that might be infected (such as game meat).
- Recently, it has been recognized that landscapers may also be at risk following an outbreak of pneumonic tularemia on Martha's Vineyard, which occurred primarily among people who were involved in mowing large areas of brush and grass. Presumably, this activity results in aerosolization either of rodent feces, dead rodents, or infected arthropods which may be in the environment.

TULAREMIA IN THE UNITED STATES: EPIDEMIOLOGY

- Tularemia cases have been reported from every state, except Hawaii. Most of the cases are occurring in the south central and western states, Missouri, Arkansas, Oklahoma, South Dakota and Montana.
- Prior to the 1950s, tularemia was considerably more common, with between 1,000 and 2,000 reported cases each year. The number of reported cases has dropped substantially over the last half a century, to the point where we now have between 100 and 200 cases reported to CDC each year.
- Currently, most of the reported cases of tularemia occur June through September, and are believed to be due to arthropod transmission. There are occasional cases occurring in the winter,

and these appear to be more common among hunters or trappers who are handling infected tissues.

- The number of cases reported to CDC between 1945 and 2002 emphasizes the fairly dramatic decrease in tularemia cases over the last 50 years. Much of this decrease really occurred without specific interventions, and may reflect a cultural change away from rabbit hunting and similar exposures that were probably more common earlier in the last century.
- The geographic distribution of reported tularemia cases from 1990 through 2000 shows that more than half of all cases are reported from four states: Arkansas, Missouri, Oklahoma, and South Dakota. And as alluded to earlier, there is an interesting focus of cases on Martha's Vineyard in Massachusetts. This is thought to have originated from the importation of cottontail rabbits to the island in the 1930s.
- Among the various ethnic groups, American Indians have, by far, the highest incidents of tularemia infections. This is thought to be related to their higher exposure, especially to ticks, and perhaps also to hunting. Nevertheless, because of the considerably larger white population, the majority of cases actually occur among whites.
- The current seasonal distribution of tularemia cases (as determined by 1990 to 1998 cases in the United States) shows a summertime peak, reflecting the activity of arthropods during the warm summer months. Interestingly, this is just the opposite from what was seen before 1950. During the period 1928 through 1944, relatively few cases occurred in the summer months and a large number of cases occurred during in the winter months, when hunting of small game was far more common.

CLINICAL PRESENTATION

The clinical presentation of tularemia is extremely variable, and it depends upon the route of inoculation, the dose, and the virulence of the organism. Following an incubation period of about three to five days, patients with tularemia typically present with high fever accompanied by non-specific symptoms such as chills, headaches, myalgias, fatigue, sore throat, cough, shortness of breath, vomiting or diarrhea. A common finding of tularemia is prominent localized lymphadenopathy.

The six principal clinical syndromes of tularemia, include:

- Ulceroglandular
- Glandular
- Oculoglandular,
- Oropharyngeal
- Typhoidal
- Pneumonic or pulmonary

These different forms relate to the mode of transmission. Ulceroglandular tularemia is by far the most common form, accounting for approximately 45 to 85 percent of reported cases. It typically results from inoculation into the skin, either through the bite of an arthropod or through handling of contaminated animals or meat. Sometimes hunters will describe cutting themselves while attempting to butcher an animal, and then developing an ulcer at the site, followed by regional lymphadenopathy. Oropharyngeal tularemia is acquired primarily through eating contaminated food or drinking contaminated water. Patients develop ulcers in the oropharynx and cervical lymphadenopathy. Pneumonic tularemia is often secondary to some other form of tularemia, but it can also occur through primary respiratory exposure.

Photographs are available that show an ulcer on the thumb of the patient with ulceroglandular tularemia with a large lymph node up in their axilla. There is also one of a patient with cervical lymphadenopathy

due to oropharyngeal tularemia, and a chest radiograph for a patient with pulmonary tularemia. This provides a visual of the diverse range of syndromes that may be seen.¹

LABORATORY DIAGNOSIS

The clinical diagnosis of tularemia is confirmed by isolation of *Francisella tularensis*. Clinical suspicion is critical in directing the selection of the correct culture media, as well as ensuring the safety of laboratory workers. In addition, materials such as swabs from ulcers or wounds, lymph node aspirates, or tissue can be examined by direct fluorescent antibody. There are serologic assays, although these are generally less useful in the acute diagnosis.

The characteristics that should lead clinical laboratories to suspect *Francisella tularensis* include:

- Poorly staining Gram-negative rods
- Compatible exposure
- Compatible clinical syndrome

The organism is slow growing, requiring up to 72 hours, and may be difficult to recover in automated culture systems. Isolates that fit these characteristics should be referred to state laboratories for further work up and evaluation.

There are more specialized tests that can be performed at reference laboratories to presumptively identify *Francisella tularensis*. The most commonly used and available test is DFA or direct fluorescent antibody. In addition, a single positive serum sample is also used as presumptive diagnosis for tularemia.

Definitive confirmation of tularemia is based on recovery of an isolate grown on cysteine heart agar with the following characteristics: grows well at 37 degrees, but poorly at 25 degrees Celsius; has characteristic of colonial morphology; and tests positive by direct fluorescent antibody. Biochemical testing is considered supplemental.

Alternately, confirmation of tularemia can be based on a four-fold (or greater) titer change in paired sera, taken at least two weeks apart, with at least one of these titers being greater than 1:160 by tube agglutination, or 1:128 by microagglutination.

TREATMENT

- Aminoglycosides are bacteriocidal for *Francisella tularensis* and are generally considered the drug of choice. Streptomycin, which is FDA approved for this indication but not always available, is given for 7 to 14 days. Alternately, gentamicin can be used and has been shown to be quite effective, although it is not FDA approved for this particular indication.
- Other medications that are effective *in vitro* or clinically include doxycycline, ciprofloxacin, and possibly levofloxacin. Tetracycline and chloramphenicol are bacteriostatic. They have been used to treat tularemia; but have been associated with relapses. In general, it's recommended that patients treated with these drugs receive up to three weeks to prevent relapse. Beta-lactams, cephalosporins are not effective for treating tularemia. Some of these, such as ceftriaxone, have *in vitro* activity that does not seem to correlate with clinical efficacy.

PROPHYLAXIS

- The issue of prophylaxis comes up periodically, particularly when laboratory workers have been exposed to tularemia. Antibiotic prophylaxis is generally not recommended following exposure. Instead, we recommend that exposed persons be placed on a fever watch, checking their

¹ For accompanying PowerPoint presentation, please contact COCA@cdc.gov and reference the tularemia presentation of April 27, 2004.

temperature every 6 hours during the incubation period. If they develop fever, antibiotics should be initiated promptly.

INFECTION CONTROL FOR PATIENTS

- Infection control is a frequently raised concern, particularly in the context of mass casualties following a BT attack. Since there has been no human-to-human transmission of tularemia, standard precautions are considered to be appropriate. Isolation of patients is not necessary and really not recommended and may impede care.
- As for bodies and clothing, bodies can be handled using standard precautions with the caveat that autopsy procedures likely to produce aerosols, such as sawing, should be avoided or conducted with careful respiratory precautions. Clothing and other materials stained with body fluids can be disinfected using standard procedures.

INFECTION CONTROL FOR THE LABORATORY

- It's important to alert microbiology laboratory personnel when *F. tularensis* is suspected, because it can pose a risk to personnel. Generally, routine diagnostic procedures can be performed under BSL-2 conditions. However, BSL-3 conditions are necessary during activities where aerosols or droplets may be generated, such as centrifuging or grinding or growing cultures on plates. Specimens presumptively identified in routine BSL-3 clinical labs should be immediately forwarded to BSL-3 reference laboratories for confirmation and further identification. State public health laboratories and/or the CDC's laboratory provide confirmatory testing.

PREVENTION

Prevention is fairly straightforward, and in reference to ticks and to animal products exposure. It is generally recommended that people:

- Avoid tick-infested areas, if possible
- Use protective clothing or repellants
- Conduct tick checks regularly after being in tick-infested areas
- Wear gloves and masks when handling wild animals, particularly rabbits (and particularly, in a setting where there has been a die-off of the animals)
- Cook wild game thoroughly to prevent ingestion of contaminated meat
- Take standard precautions for handling drainage from wounds or eyes of patients with tularemia to protect hospital workers

THREAT OF BIOLOGICAL WARFARE

- Interest in tularemia has been renewed by the threat of biological warfare. In a WHO study done in the 1970s, it was estimated that 50 kilograms of aerosolized *F. tularensis* dispersed in a line of two kilometers upwind of a population center (under ideal weather conditions) could kill up to or over 150,00 people. Please note that ideal conditions are something that is rarely seen, so situation would probably be unlikely to happen. Nevertheless, it does emphasize the potential.
- There's also concern that following such a release, the organism would get into local mammals and ticks and be propagated and maintained in an area where it was not previously common. In addition, contamination of the water supply is of some concern.

I will end with this last quotation from Parker from 1934, which is sort of the classic quotation for tularemia. He says, "*I know of no other infection of animals communicable to man that can be acquired from sources so numerous and so diverse. In short, one can but feel the status of tularemia, both as a disease in nature and of men is one of potentiality.*"

QUESTION AND ANSWER SESSION

Dr. Dan Baden:

Dr. Mead, you mentioned that some of the organisms that were modified for bioweapon use had streptomycin resistance. I thought I heard this at least. In that case, what would be the drug of choice to use?

Dr. Paul Mead:

Well there are several alternatives as mentioned there, and they could include fluoroquinolones, such as ciprofloxacin. Doxycycline would be another alternative. Whether or not cross-resistance to streptomycin would pertain to gentamicin, I'm not entirely sure, but it may be that gentamicin would nevertheless be effective. That's probably the reason why it would be important to get susceptibility testing, particularly if there is any concern in the setting of a bioterrorist event. This is because the organism can be modified. And presumably, someone who went to the effort to intentionally produce and release such an organism might have also engineered some resistances. Although saying that, I think we sometimes overestimate the effort that people put into engineering these things, as indicated by some past events.

Dr. Dan Baden:

You mentioned current clusters. Would you elaborate?

Dr. Paul Mead:

- Over the last few years, we've had a number of outbreaks or clusters that are perhaps notable. The first I alluded to was the outbreak of tularemia on Martha's Vineyard, involving some landscapers. An investigation was done in conjunction with the Massachusetts Department of Health and other local and state health officials, which essentially identified mowing brush as a likely source of exposure. Interestingly, a serologic survey was done after that, showing that approximately 10% of landscapers working on Martha's Vineyard were sera positive for tularemia, some of whom remembered having illness and some of whom did not. This suggests tularemia can be a milder illness in some people and that people who are exposed to mowing and cutting of brush may be infected more often than previously recognized.
- This is also driven home by a recent cluster of cases last summer in another state, in which some boys with a lawn-mowing service mowed over a dead rabbit that they found on a lawn, reportedly as a way of cleaning up the rabbit. They both developed significant pulmonary infections and had to be hospitalized. What I think is perhaps interesting about this particular cluster is that their father, who maintained the lawn mowers, and was not present at the time the mowing occurred, also developed significant pulmonary tularemia. As far as we can tell, this was linked to the fact that he used an air hose to blow dust off of the lawn mowers at the end of each day, creating a plume of material, which we believe had remnants of the rabbit (and *Francisella tularensis*), and led to his infection.
- The third turn of events is notable, but may not have been as widely recognized. This concerns widespread distribution of commercial prairie dogs infected with tularemia, which I believe occurred two years ago. Dr. Peterson can probably provide more details on that than I can. Essentially, it was discovered that prairie dogs being distributed around the country through pet were infected and dying of tularemia. This particular outbreak in prairie dogs really presaged what happened last year with monkey pox. It was much the same distribution and many of the same issues of infected animals being sent across state lines.

- Fortunately, following the monkey pox event, the shipment of prairie dogs for that purpose is no longer possible. It has been banned in the United States. So those are just three clusters or outbreaks that we've worked on in the recent past. These are helping us to better define the epidemiology of this disease.

Dr. Dan Baden:

I have a third question, if we could. In some scenarios of use of a bioweapon, like the one you outlined in the ideal conditions, people may not know until patients start showing up with symptoms. Is there any concern or do people who have relatively advanced disease respond fairly well to antibiotic treatment with tularemia?

Dr. Paul Mead:

Well, that's a little bit hard to say because the bioterrorism scenarios are often somewhat different than what you would expect to see normally. Again, tularemia can be a fairly mild illness that patients can have for a while, but under this scenario, it's presumed that people would have a large exposure to an aerosolized form of tularemia. When you look across the various clinical syndromes of tularemia, certainly pneumonic tularemia has a considerably higher fatality rate, at least without antibiotics, than the other forms of tularemia. Currently, this mortality rate due to naturally occurring tularemia in the United States is under 2%. However, in the absence of antibiotics, pulmonary tularemia can be considerably more fatal, resulting in 50% or so mortality. Whether or not that would happen or whether the rate would be higher following a BT event would again depend a bit upon the dose that people were exposed to, whether or not it had been engineered to have additional virulence factors, whether or not it was antibiotic resistant.

I think in general, it's reasonable to say that early appropriate treatment improves outcome in most infectious diseases and in tularemia. It's a little bit less like plague where getting therapy early is critical. Nevertheless, if the patient is already in critical condition when diagnosed, they will likely have a higher mortality rate.
